

An overview of commonalities in the mechanisms underlying gambling and substance use disorders

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1 An overview of commonalities in the neurobiological and psychological underpinnings of
2 gambling and substance use disorders

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Starting in the DSM-5, both drug and gambling addictions are discussed in a single chapter, entitled 'Substance-Related and Addictive Disorders'. The next version of the World Health Organization's International Classification of Diseases (ICD-11), which is due to be released in 2022, also classifies gambling as an addiction and goes further by categorizing where the maladaptive behavior occurs – predominately 'offline' or 'online'. Such descriptions mark changes from earlier versions of these publications, in which gambling was considered an impulse control disorder, rather than an addiction (DSM-IV & ICD-10). The convergent evolution of how these conditions are defined and diagnosed is primarily supported by recent research outlining how the development, expression, and effective treatment of drug and gambling addictions share similar biopsychosocial underpinnings. Yet, there are some crucial differences between drug use and gambling disorders that require further investigation.

This special topic issue of *Progress in Neuro-Psychopharmacology and Biological Psychiatry* explores novel common (and divergent) pathways linking gambling and drug addictions, through empirical reports and critical reviews, human and animal studies, and assessments of psychological and neuronal mechanisms. The goals of this special issue are to integrate developments in these diverse areas of study, to raise the possibility of unified treatments for addiction, and to provide a deeper understanding of how altered biological pathways (e.g., mesocorticolimbic, neuroendocrine) contribute to psychological and behavioral dysfunction.

In this issue, Grant and Chamberlain (2020) compare clinical similarities and differences between gambling disorder (GD) and substance use disorders (SUDs). They describe how people with either of these conditions may have difficulty inhibiting or controlling their behavior, which is characteristic of high levels of impulsivity and risk-taking (Grant and Chamberlain, 2020). Grant and Chamberlain mention, however, that while there may be substantial overlap between GD and SUDs, the biopsychosocial underpinnings of these disorders can vary across individuals. It is believed that comorbidity between mental health conditions may account for some of this individual variation (Balodis and Potenza, 2020; Grant and Chamberlain, 2020). Such variation in behavior is also seen in animal models, which are highlighted in several articles in this special issue (Anselme and Robinson, 2020; Oggiano et al., 2020; Orsini et al., 2020). For example, Orsini *et al.* (2020) demonstrate that rats exhibiting heightened risk-taking are more likely to escalate drug-pursuit (during long-access drug self-administration), compared to animals that are risk-averse. Conversely, using a rat gambling task and pharmacologic magnetic resonance imaging (phMRI), Oggiano *et al.* (2020) report decreases in the pursuit of

uncertain options in a subset of animals that show ADHD-like behaviors; this finding was accompanied by differential activation in striatal sub-regions.

In their review article, Balodis and Potenza (2020) suggest that reduced inhibitory control over behavior by the medial prefrontal (mPFC) and dorsal anterior cingulate (dACC) cortices can contribute to substance use and gambling addictions. Blunted behavioral regulation may be a consequence of how strongly drug- or gambling-related cues can alter mPFC/dACC activity (Balodis and Potenza, 2020). Another region that is often ‘turned on’ by reward-associated cues is the nucleus accumbens (NAc; Linnet, 2020; Zack et al., 2020), a region of the ventral striatum that receives dopaminergic input from the ventral tegmental area (VTA). Excitation of the NAc may be associated with elevated craving for reward (Balodis and Potenza, 2020) and the activity of the NAc itself can be modulated by a variety of brain regions (e.g., mPFC and amygdala). For example, in this special issue van Holstein *et al.* (2020) demonstrate how disconnecting the basolateral amygdala from the NAc results in suboptimal decision-making in rodents during a gambling task.

Two articles in the special issue discuss the role of dopamine in the NAc for drug use and gambling disorders (Linnet, 2020; Zack et al., 2020). Both articles explain how dopamine neurotransmission may facilitate learning about stimuli that predict reward (either for drugs or monetary gain). As discussed above, there is individual variation in behavior and neurochemical responses observed in individuals with a SUD or GD. Some individuals, for example, may display an exaggerated response to reward-associated cues. This can take the form of excessive approach (‘sign-tracking’) to the cue itself, enhanced motivation evoked by cue exposure, and significant dopamine release after experiencing a cue (Anselme and Robinson, 2020).

It can be challenging to compare the brain responses directly caused by drugs with the receipt of monetary rewards in gambling. This is because the pharmacological action of some substances is to enhance dopamine transmission in the NAc; this can also result in long-lasting brain plasticity. For example, repeated exposure to drugs can enhance (sensitize) the ability of the drug to increase dopamine release in the NAc (Linnet, 2020). At the same time, hypoactivation of certain brain regions may be observed in the absence of drug or drug cues (Linnet, 2020; as argued by Leyton and Vezina, 2014). Furthermore, as demonstrated by Robinson *et al.* in this special issue, sensitization produced by repeated exposure to drugs of abuse can bias an individual’s attraction towards cues that are highly predictive of reward

(rather than directing attention to gambling-like stimuli which have less predictive value; Robinson et al., 2020).

Despite these comparative challenges, intermittent exposure to unpredictable non-drug reward has been found to sensitize dopamine responsivity in the brain (reviewed by Mascia et al., 2020). This process might cause cues that are associated with non-drug reward to become more motivational (Anselme and Robinson (2020) focus on enhanced sign-tracking), thereby driving gambling-like behavior by instilling a sense of ‘cognitive appetite’ that requires resolution (Zack et al., 2020). Indeed, in an animal model in which rats are repeatedly and intermittently exposed to uncertain conditions of non-drug reward, dopamine transmission in the NAc becomes sensitized, and rats develop addiction-like pursuit of amphetamine (Mascia et al., 2020). Notably, these effects parallel what is observed following exposure to sensitizing drug regimens (Mascia et al., 2020). Thus, aberrant reward-learning, repeated exposure to uncertainty, and potential pharmacological effects of drugs can summate in a “constellation of events [that] can disturb the finely-tuned neurocircuitry that guides adaptive behaviour” (Zack et al., 2020) by altering dopamine neurotransmission in the brain.

Thus far we have discussed how exposure to distinct events (e.g., experience with reward or reward-related cues that are either unpredictable or intermittent) may quickly enhance dopamine neurotransmission in certain brain regions, thereby exciting certain behaviors or cognitive states that promote reward-pursuit. The brief spikes in dopamine neurotransmission caused by such rapid and definable occurrences are often referred to as ‘phasic dopamine signalling’. In contrast, dopamine neurons are also believed to have another type of activity state in which they display prolonged, or tonic, levels of action potential firing and subsequent transmitter release (although, this remains an area of debate; see Hamid et al., 2016). It is thought that such long-lasting elevations of extracellular dopamine may encourage a state of vigor in the individual – this could also motivate the pursuit of reward. In this special issue, Kirschner *et al.* (2020) describe how vigor related to enhanced tonic dopamine levels is associated with “compulsive engagement with rewarding stimuli, increased risk taking and impulsivity”. Such a state, which may be observed in people with psychosis or bipolar disorder, could lead to substance misuse and problematic gambling (Kirschner et al., 2020). In another example, when people with Parkinson’s Disease (who have low levels of dopamine) are treated with certain dopamine-replacement therapies (such as agonists for dopamine D2/D3-type receptors), there is sometimes an increase in impulsive behaviors, like gambling (Kirschner et al., 2020; Napier et al., 2020). In this special issue, Napier *et al.* (2020) suggest that these

dopamine agonists mimic tonic dopamine neurotransmission in patients, and they highlight studies demonstrating how this could lead to disadvantageous decision-making (as displayed during gambling).

While most research has focused on similarities in dopamine function between SUDs and GD, the activation or repression of other biological processes are also implicated in these conditions. For example, in this special issue, Mascia *et al.* (2020) show that extracellular levels of glutamate, adenosine, and aspartic acid are also increased in the NAc of rats exposed to uncertain non-drug reward. The importance of glutamate in the NAc to gambling-like behavior in rats is also demonstrated by van Holstein *et al.* (2020), specifically the BLA-NAc shell glutamate pathway in perturbed decision making. It is reflected as well in rats previously exposed to repeated intermittent uncertainty by altered levels of several proteins (CaMKII, PKC, Δ FosB, GLT1) known to regulate glutamate transmission (Mascia *et al.*, 2020). In other brain regions, levels of the neurotransmitter acetylcholine may help govern attention to reward-associated stimuli; this may be disrupted in GD and SUD, as shown in the sign-tracking animal model (Anselme and Robinson, 2020).

Differential hormonal signalling may also contribute to GD and SUDs. In this special issue, Li *et al.* (2020) review the contributions of the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes to alcohol use disorder and GD. For example, they describe how testosterone may be enhanced by alcohol use and gambling, while cortisol may have divergent effects on these behaviors (increasing alcohol consumption and decreasing gambling; Li *et al.*, 2020). Regardless of these similarities and differences, Li *et al.* also emphasize that substantial individual variation exists in hormonal function and that various psychosocial factors impact desire to gamble or drink alcohol. Furthermore, future studies should investigate how sex differences uniquely impact biological processes that drive gambling and drug use.

Finally, there are specific differences between SUDs and GD that are difficult to reconcile within a unified model of addiction. In essence, these include attempts to recover monetary losses that result from gambling and high rates of suicidal ideation in gamblers (Grant and Chamberlain, 2020). Balodis and Potenza, for example, suggest that different brain circuits are recruited during “loss chasing” tasks performed by gamblers and cocaine-dependent individuals; such findings indicate that certain behaviors and neural processes are not shared between these conditions. When considering these findings, it is also important to remember that few human brain imaging studies *directly* compare individuals who have a SUD or GD (in

most examples, separate research projects investigate SUD or GD in comparison to ‘healthy’ controls).

We started this introduction to our special issue on problematic gambling and drug use by describing how diagnostic criteria for these conditions are converging – according to the newest version of the DSM and the updated ICD-11, gambling disorder is categorized as an addiction along with various substance use disorders. The articles in this special issue largely support the new diagnostic criteria by providing evidence of similar biopsychosocial underpinnings of these conditions. While much attention has been placed on the role of dopamine neurotransmission within the NAc, the articles show that other brain regions and signalling molecules are also implicated in SUDs and GD, and thus may also serve as pharmacotherapeutic targets. The studies presented within this special issue also stress how individuals vary in why they gamble or use drugs, and therefore may require personalized treatments. Some individual differences, for example, may relate to sex hormone signalling or comorbidities amongst psychiatric conditions – such variation requires further investigation. Finally, researchers have observed unique behavioral patterns and cognitive states in people who pathologically pursue drug or excessively gamble; these differences may be difficult to reconcile in a unified theory of addiction. Despite these challenges, this collection of articles provides novel insights into both the shared and divergent features of substance use and gambling disorders. By bringing together research on SUDs and GD from scientists with unique specializations and opinions, we believe that this special issue will meaningfully contribute to the study of addiction, encourage cross-topic collaboration, and positively impact treatment for these conditions.

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